PATENT COOPERATION TREATY

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From the INTERNATIONAL	SEARCHING	AUTHORITY
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Patent Division

To: NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL WOOD, Dan L. P.O. Box 6288 SEARCHING AUTHORITY, OR THE DECLARATION Indianapolis IN 46206-6288 UNITED STATES OF AMERICA (PCT Rule 44.1) Date of mailing (day/month/year) 27/07/2005 Applicant's or agent's file reference FOR FURTHER ACTION See paragraphs 1 and 4 below X-16949M ✓ International application No. International filing date (day/month/year) PCT/US2005/010240 ✓ 25/03/2005 Applicant ELI LILLY AND COMPANY

1.	x	The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
		Filing of amendments and statement under Article 19:
		The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):
		When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.
		Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41–22) 740.14.35
		For more detailed instructions, see the notes on the accompanying sheet.
2.		The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3.		With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
		the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices. no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4.	Rem	ninders
	Inter	rtly after the expiration of 18 months from the priority date, the international application will be published by the rnational Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international ication, or of the priority claim, must reach the International Bureau as provided in Rules 90 <i>bis</i> .1 and 90 <i>bis</i> .3, respectively, ore the completion of the technical preparations for international publication.
	Inter	applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the mational Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an mational preliminary examination report has been or is to be established. These comments would also be made available to public but not before the expiration of 30 months from the priority date.
	exar date	nin 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary mination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed for entry into the national phase before those designated Offices.
		espect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 oths.
		the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's de, Volume II, National Chapters and the WIPO Internet site.

	Name and mailing address of the International Searching Authority	Authorized officer
, '	European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Federico Bonomelli

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international policiation. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been its filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

Notes to Form PCT/ISA/220 (first sheet) (January 1994)

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged,
- (ii) the claim is cancelled;
- (iii) the claim is new.
- (iv) the claim replaces one or more claims as filed,
- (v) the claim is the result of the division of a claim as filed

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- 1 [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged, new claims 49 to 51 added."
- 2 [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
 "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
 "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- 4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled, claims 14, 15 and 16 replaced by amended claim 14, claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence)

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

Notes to Form PCT/ISA/220 (second sheet) (January 1994)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER		see Form PCT/ISA/220					
X-16949M	ACTION as well as, where applicable, item 5 belo							
International application No.	International filing date (day/month	v/year)	(Earliest) Priority Date (day/month/year)					
PCT/US2005/010240 25/03/2005 01/04/2004								
Applicant								
ELI LILLY AND COMPANY								
This International Search Report has been according to Article 18. A copy is being tra			nority and is transmitted to the applicant					
This International Search Report consists	of a total of she	eets.						
X It is also accompanied by	a copy of each prior art document c	ited in this	report.					
			sis of the international application in the					
language in which it was filed, unl	ess otherwise indicated under this it	em.						
The international this Authority (Ru		of a transl	ation of the international application furnished to					
b. With regard to any nucleo	otide and/or amino acid sequence	disclosed	in the international application, see Box No. I.					
2. Certain claims were fou	nd unsearchable (See Box II).							
3. Unity of invention is lac	king (see Box III).							
4. With regard to the title ,								
X the text is approved as su	bmitted by the applicant.							
the text has been establis	shed by this Authority to read as follo	ws:						
5. With regard to the abstract,	5. With regard to the abstract,							
X the text is approved as su	• • • • • • • • • • • • • • • • • • • •		Was a standard to the second t					
the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.								
6. With regard to the drawings ,								
a. the figure of the drawings to be published with the abstract is Figure No								
as suggested by the applicant.								
as selected by this Authority, because the applicant failed to suggest a figure. as selected by this Authority, because this figure better characterizes the invention.								
	is Authority, because this tigure beτα e published with the abstract.	ei characte	enzes une invention.					
L. Line of the lightes is to b	o publiched with the aboutot.							

Form PCT/ISA/210 (first sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US2005/010240

CLASSIFICATION OF SUBJECT MATTER PC 7 C07D207/09 C07D C07D401/10 C07D403/10 C07D413/10 C07D405/10 A61K31/40 A61P25/00 A61K31/4025 A61P3/04 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC 7 CO7D A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, CHEM ABS Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No Ρ,Χ MO 2004/076412 A (SUGEN, INC; CUI, 1-11,14JINGJONG, JEAN) 10 September 2004 (2004-09-10) page 89, line 22 - line 23 WO 02/076925 A (ELI LILLY AND COMPANY; 1 - 22Α √BEAVERS, LISA, SELSAM; GADSKI, ROBERT, ALAN; HI) 3 October 2002 (2002-10-03) claims; examples 130-133, 136, 144, 209-216, 229-235, 242, 243, 25 1-255,26Α WO 03/064411 A (NOVO NORDISK A/S; 1 - 22BOEHRINGER INGELHEIM INTERNATIONAL GMBH) 7 August 2003 (2003-08-07) claims page 60 - page 61; example 28 Further documents are listed in the continuation of box C Patent family members are listed in annex Special categories of cited documents "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance invention earlier document but published on or after the international "X" document of particular relevance, the claimed invention filing date cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other, such docu document referring to an oral disclosure, use, exhibition or ments, such combination being obvious to a person skilled in the art. document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of the actual completion of the international search Date of mailing of the international search report 20 July 2005 27/07/2005 Name and mailing address of the ISA Authorized officer European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel (+31–70) 340–2040, Tx 31 651 epo nl, Fax. (+31–70) 340–3016 Kollmannsberger, M

1

International application No. PCT/US2005/010240

INTERNATIONAL SEARCH REPORT

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 15-20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/010240

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 2004076412	Α	10-09-2004	US WO	2005009840 / 2004076412 /		13-01-2005 10-09-2004
WO 02076925	Α	03-10-2002	CA EP JP WO	2441080 / 1379493 / 2004532834 02076925 /	A2 T	03-10-2002 14-01-2004 28-10-2004 03-10-2002
WO 03064411	А	07-08-2003	BR CA WO EP US ZA	0306980 / 2473468 / 03064411 / 1474419 / 2003195190 / 200405632 /	A1 A1 A1 A1	09-11-2004 07-08-2003 07-08-2003 10-11-2004 16-10-2003 17-01-2005



From the

PATENT COOPERATION TREATY

INTERNATIONAL SEARCHING AUTHORITY To: WRITTEN OPINION OF THE see form PCT/ISA/220 INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1) Date of mailing XILAYAM (day/month/year) see form PCT/ISA/210 (second sheet) Applicant's or agent's file reference FOR FURTHER ACTION see form PCT/ISA/220 See paragraph 2 below International application No International filing date (day/month/year) Priority date (day/month/year) PCT/US2005/010240 25.03.2005 01.04.2004 International Patent Classification (IPC) or both national classification and IPC C07D207/09, C07D401/10, C07D413/10, C07D403/10, C07D405/10, A61K31/40, A61K31/4025, A61P25/00, Applicant **ELI LILLY AND COMPANY** 1 This opinion contains indications relating to the following items: Box No. I Basis of the opinion Box No. II Priority ☑ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability □ Box No. IV Lack of unity of invention Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial Box No ∨ applicability: citations and explanations supporting such statement ☑ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application Box No. VIII Certain observations on the international application **FURTHER ACTION** 2. If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66 1 bis(b) that written opinions of this International Searching Authority will not be so considered If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later For further options, see Form PCT/ISA/220. For further details, see notes to Form PCT/ISA/220. Name and mailing address of the ISA Authorized Officer



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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US2005/010240

	Вох	No. I	Basis of the opinion
1.			d to the language , this opinion has been established on the basis of the international application in ge in which it was filed, unless otherwise indicated under this item.
		langua	pinion has been established on the basis of a translation from the original language into the following age , which is the language of a translation furnished for the purposes of international search Rules 12.3 and 23.1(b)).
2.	With	regar essary	d to any nucleotide and/or amino acid sequence disclosed in the international application and to the claimed invention, this opinion has been established on the basis of:
	a. ty	pe of r	naterial:
] as	equence listing
] tab	le(s) related to the sequence listing
	b fo	rmat o	f material:
] in v	vritten format
] in c	computer readable form
	c. tır	ne of f	iling/furnishing:
		Co	ntained in the international application as filed.
] file	d together with the international application in computer readable form.
		3 fur	nished subsequently to this Authority for the purposes of search.
3		has be copies	ition, in the case that more than one version or copy of a sequence listing and/or table relating thereto een filed or furnished, the required statements that the information in the subsequent or additional is is identical to that in the application as filed or does not go beyond the application as filed, as oriate, were furnished
4.	Add	itional	comments.
_	Вох	No. II	Priority
1.		does r	alidity of the priority claim has not been considered because the International Searching Authority not have in its possession a copy of the earlier application whose priority has been claimed or, where ed, a translation of that earlier application. This opinion has nevertheless been established on the applicant that the relevant date (Rules 43 <i>bis</i> .1 and 64.1) is the claimed priority date.
2.		has be	pinion has been established as if no priority had been claimed due to the fact that the priority claim een found invalid (Rules 43 <i>bis</i> .1 and 64.1). Thus for the purposes of this opinion, the international late indicated above is considered to be the relevant date.
3.	Add	itional	observations, if necessary:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No. PCT/US2005/010240

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability						
	The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:					
	the entire international application,					
M	claims Nos. 15-20					
bec	ause:					
	the said international application, or the said claims Nos. 15-20 relate to the following subject matter which does not require an international preliminary examination (specify):					
	see separate sheet					
	the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify)					
	the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.					
	no international search report has been established for the whole application or for said claims Nos.					
	the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:					
	the written form		has not been furnished			
			does not comply with the standard			
	the computer readable form		has not been furnished			
			does not comply with the standard			
	the tables related to the nucleot not comply with the technical re	ide a quire	and/or amino acid sequence listing, if in computer readable form only, do ements provided for in Annex C-bis of the Administrative Instructions.			
	See separate sheet for further details					

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

1-22

No: Claims

Inventive step (IS)

Yes: Claims

1-22

No: Claims

Industrial applicability (IA)

Yes: Claims

1-14,21,22

No: Claims

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 15-20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1. State of the art:

- D1: WO 2004/076412 A (SUGEN, INC; CUI, JINGJONG, JEAN) 10 September 2004 (2004-09-10)
- D2: WO 02/076925 A (ELI LILLY AND COMPANY; BEAVERS, LISA, SELSAM; GADSKI, ROBERT, ALAN; HI) 3 October 2002 (2002-10-03)
- D3: WO 03/064411 A (NOVO NORDISK A/S; BOEHRINGER INGELHEIM INTERNATIONAL GMBH) 7 August 2003 (2003-08-07)

D1 is P-document and will be disregarded during the PCT procedure.

In the following paragraphs references to the above documents relate to the parts indicated in the search report unless specified otherwise.

V-2. Novelty (Art. 33(2) PCT)

The claims differ from the compounds disclosed in D2 on account of the second aryl ring and from the compounds of D2 due to the absence of the ethylene spacer.

The claims fulfil Art. 33(2) PCT).

V-3. Inventive step (Art. 33(3) PCT)

Closest prior art is seen in D2 since D2 also discloses selective histamine H3 antagonists with a similar structure. The presently claimed compounds differ from the compounds disclosed in D2 in the addition of a second aryl ring. The problem to be solved was to find further compounds presenting this activity. D3 discloses biaryl compounds as histamine H3 antagonists, however, the biaryl part is separated from the pyrrolidinopyrrolide part by an ethylene spacer. It is not considered obvious to a man skilled to add a second aryl ring to the compounds of D2 in order to obtain further histamine H3 antagonists.

The claims also fulfil Art. 33(3) PCT.

Re Item VI Certain documents cited

Certain published documents

Application No	Publication date (day/month/year)	Filing date	Priority date (valid claim)
Patent No		(day/month/year)	(day/month/year)
WO2004/076412	10.09.2004	26.02.2004	26.02.2003